UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,933	09/14/2005	Shangguan Tong	TRA-027.01	1561

25181 7590 03/06/2008

FOLEY HOAG, LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BLVD
BOSTON, MA 02110

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
03/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,933	TONG ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34,36-69,71-142,144-151 and 153-168* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34,36-69,71-142,144-151 and 153-168* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 1/22/08.

Claims 35 and 152 were canceled.

Claims 1-34, 36-69, 71-142, 144-151, and 153-168 remain pending and are under consideration.

This Action is NON-FINAL due to new grounds of rejection not necessitated by Applicant's amendment. Rejections not reiterated are withdrawn.

Oath/Declaration

The oath or declaration stands objected to as defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specifically, the name and citizenship of Shangguan Tong were altered, but the alterations were not initialed or dated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147, and 153-168 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopolous et al (US Patent 4,235,871) in view of Kikuchi et al (US 4,687,661) and Meers et al (US Patent 6,120,797).

Papahadjopolous taught a variety of liposomes comprising nucleic acids such as DNA or RNA. See column 3, lines 28-40; column 6, lines 31-43; column 8, lines 45-68 column 13, lines 59-67; and claims 16 and 17. The liposomes may consist of a fusogenic lipid such as dioleoylphosphatidylethanolamine (DOPE) or phosphatidylserine (PS), and may also comprise a variety of other lipids including cholesterol, see paragraph bridging columns 3 and 4. PS is a fusogenic lipid.

Papahadjopolous taught a method of making liposomes by combining lipids as discussed above and nucleic acids in an inert to form an emulsion, thereafter forming a gel, and finally converting the gel to a suspension of liposomes by addition of an aqueous medium. See entire document, especially e.g. claim 1, and column 4, line 45 to column 6, line 30.

Regarding claim 89, Papahadjopolous taught addition of an aqueous solvent to the gel, rather than addition of the gel to an aqueous solvent, but this detail is considered to be a simple matter of design choice, and is therefore an obvious variant of the method of Papahadjopolous.

Regarding claims 111-122 and 146, Papahadjopolous is silent as to the total amount of lipid forming and fusogenic lipid expressed as a weight-percent of the gel, but the amounts of these lipids are considered to be result-effective variables that are

obvious to optimize in order to modulate the characteristics of the resultant liposomes. See e.g. column 4, lines 53-58; and column 6, lines 11-18 and 28-34.

Regarding claims 124-135, Papahadjopolous is silent as to the ratio of the weight of the increment of aqueous medium that can be used to wash the gel, and the weight of the gel itself. However, this is a parameter that would be routinely optimized by one of ordinary skill, see e.g. column 4, lines 53-58.

Regarding claims 136-140, Papahadjopolous is silent as to the total amount of nucleic acid expressed as a weight-percent of the gel, but the amounts of the nucleic acid is clearly a result-effective variable that is routinely optimized by one of ordinary skill. in order to modulate the characteristics of the resultant liposomes. See e.g. column 6, lines 11-18 and 28-34.

Instant claim 145 requires that the gel or gel particles lack a hydrating agent, and that no hydrating agent is used in step A of the method. The specification defines a hydrating agent at paragraph 74 as a compound having at least two ionizable groups, one of which ionizable groups is capable of forming an easily dissociative ionic salt, which salt can complex with the ionic functionality of the liposome-forming lipid. Papahadjopolous exemplifies the use of buffers comprising histidine and TES, both of which appear to meet the definition of a "hydrating agent". However, Papahadjopolous did not require that the aqueous phase added to the lipids must be buffered, but only that it comprises the biological agent to be encapsulated. The inclusion or exclusion of a buffering agent in the aqueous phase is a matter of design choice, as is the selection of any particular buffering agent. It would have been obvious to one of ordinary skill in

the art to either include in, or exclude from, the aqueous phase an ionizable agent such as a buffer. If one chose to include a buffer, it would have been obvious to use any known biological buffer, including monoionic buffers such as imidazole.

Regarding claim 146, Papahadjopolous is silent as to the total amount of organic solvent remaining in the gel, but it is clear that this is a result-effective variable that is routinely optimized by one of ordinary skill. See e.g. column 4, lines 53-58.

Papahadjopolous did not teach a water miscible organic solvent or N-acyl phosphatidylethanolamines.

Kikuchi taught that the use of volatile organic solvents for dissolution of lipids in methods of making liposomes was problematic because these organic solvents tend to remain in the final preparation and can be harmful to human health. Kikuchi suggests the use of water miscible organic solvents, such as ethylene glycol, for dissolution of lipids in methods of preparing liposomes. See column 1, line 60 to column 2, line 14; and column 2, lines 42-50.

Meers taught N-acyl phosphatidylethanolamines, including a N-dodecanoyl dioleoyl phosphatidylethanolamine, for use in liposome formation. See e.g. abstract; and column 4, lines 40-51.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the water miscible solvent of Kikuchi in the method of Papahadjopolous because Kikuchi taught that the use of water miscible organic solvents was safer for applications in which the product liposomes were to be used in vivo. It would have been similarly obvious to use the lipid of Meers in the liposomes of

Papahadjopolous because Meers taught that it promotes membrane fusion. See e.g. column 1, lines 48-60.

Thus the invention as a whole was prima facie obvious.

Claims 17-24, 26-28, 32, 91-98, 100, 101, 105, and 148-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopolous, Kikuchi, and Meers, as applied to claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-151, and 153-168 above, and further in view of Eppstein et al (US Patent 4897355) taken with the evidence of GenBank Accession No. M77788.

The teachings of Papahadjopolous, Kikuchi, and Meers are summarized above and render obvious methods of making liposomes comprising nucleic acids and N-acyl phosphatidylethanolamine lipids by solubilizing liposome-forming lipids in a water miscible organic solvent.

These references did not specifically teach plasmid DNA or oligonucleotides or the use of DOPE or DOPC.

Eppstein taught that liposomes could be used to encapsulate and deliver to cells plasmid DNAs and oligonucleotides, including pSVCAT (5 kbp) and oligonucleotides of an average length of about 130 bp. See column 3, lines 56-59; column 8, lines 32-40 and 43-45; column 10, lines 56-59; column 48 lines 24-50, and paragraph bridging columns 48 and 49. GenBank Accession No. M77788 provides evidence that PSVCAT is 5003 base pairs in length.

Eppstein also taught a variety of lipids that could be used to form liposomes including dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine, and cholesterol (see paragraph bridging columns 7 and 8; column 16, lines 53-and 54; and column 38, line 37).

Eppstein also taught methods of transfecting eukaryotic cells in vitro at 37°C (column 45, lines 43-52), as well as intravenous delivery to humans (see column 8, lines 1-13; column 10, lines 37-62; column 12, lines 48-53; column 13, lines 27-29; and column 20, lines 21-41).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of Papahadjopolous as modified by Kikuchi and Meers to encapsulate the plasmid or oligonucleotides of Eppstein because Papahadjopolous suggests that the liposomes will protect nucleic acids from degradation (see e.g. column 13, lines 59-67), and because one of ordinary skill would clearly appreciate their utility for this purpose in view of the teachings of Eppstein. It would have been similarly obvious to use the lipids of Eppstein in the methods of Papahadjopolous, because MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. In this case the lipids of Eppstein are clearly suitable for making liposomes. Finally it would have been obvious to use the liposomes to transfect eukaryotic cells in vitro or in vivo, as well as for intravenous delivery in humans because this was suggested by Eppstein.

Claims 82-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Papahadjopolous, Kikuchi, and Meers, as applied to claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147, and 153-168 above, and further in view of Lenk et al (US Patent 5,169,637).

The teachings of Papahadjopolous, Kikuchi, and Meers are summarized above and render obvious methods of making liposomes comprising nucleic acids and N-acyl phosphatidylethanolamine lipids by solubilizing liposome-forming lipids in a water miscible organic solvent.

The combined references did not specifically teach acetone, ethanol, methanol, or 2-propanol as water-miscible organic solvents.

Lenk taught a variety of solvents that cold be used to solubilize lipids, including acetone, ethanol, methanol, or 2-propanol. See table VI at column 40.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use in the invention of Papahadjopolous any water miscible organic solvent that can be used to solubilize liposome-forming lipids in view of the teachings of Kikuchi, as discussed above. It would have been obvious to use acetone, ethanol, methanol, or 2-propanol because Lenk taught that these can be used to solubilize lipids. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635